REMARKS/ARGUMENTS

With this amendment, claims 1-6, 8, 9, 19, and 42-53 are pending. Claims 7, 19, 21-29, 31-41, and 54-80 are withdrawn. Claims 10-18, 20, and 30, are cancelled. For convenience, the Examiner's rejections are addressed in the order presented in a March 14, 2006, Office Action.

I. Status of the claims

Claim 1 is amended to recite that the ADNF I polypeptide has neurotrophic/neuroprotective activity. Support for this amendment is found throughout the specification, for example at page 9, lines 22-27. Claim 42 is amended to depend from claim 1, and claims 43-44 and 46-52 are amended to correct related dependency issues. Reference to the ADNF III polypeptide remains solely to preserve Applicants' right to rejoinder. All of pending claims 42-53 require the ADNF I polypeptide of claim 1 and include the limitations of claim 1. These amendments add no new matter.

Various withdrawn claims are amended to depend from claim 1 and to maintain Applicants' right to rejoinder of withdrawn claims. These amendments add no new matter.

II. Amendments to the specification

The Office Action objected to the presence of hyperlinks in the specification. In order to expedite prosecution, Applicants have amended the specification accordingly and believe that all hyperlinks are now deleted.

III. Claim objections

Claims 42 and 49-52 are objected to because the claims allegedly contain non-elected subject matter. Applicants have amended claim 42 to depend from claim 1. Claims 49-52 are amended to depend from claim 42 in order to include the limitations of claim 1 in each claim and to maintain the right to rejoinder for the Applicants.

Dependent claim 5 is objected to as allegedly failing to further limit claim 1. In order to expedite prosecution, claim 5 is now amended to recite "wherein the ADNF I polypeptide **consists of** Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala (SEQ ID NO:1)."

In view of the above amendments, withdrawal of the objections to the claims is respectfully requested.

IV. Rejections under 35 U.S.C. §103(a)

According to the Office Action, claims 1-6, 8-9, 42-45, and 49-53 are rejected as allegedly obvious over Brenneman (US Patent No. 6,174,862), Voet *et al.* (1995) and Goodman (US Patent No. 4,587,046). According to the Office Action, Brenneman teaches administration of the ADNF I protein to reduce neuronal cell death; Voet *et al.* teaches that D-amino acids are more resistant to proteolysis than are their L-amino acid counterparts; and Goodman teaches that peptides comprising D-amino acids are more resistant to proteolysis than are their L-amino acid counterparts. To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

The Office Action has not established a case of *prima facie* obviousness. To establish a case of *prima facie* obviousness, the Examiner must meet three basic criteria:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). M.P.E.P. §§ 706.02(j) and 2143.

The references cited by the Examiner fail to provide a reasonable expectation of success in practicing the invention and fail to provide a motivation for the combination of the references. In addition, the references cited by the Examiner fail to provide all the elements of the rejected claims. Voet *et al.* teaches only the definition of D amino acids are and that they are components of many antibiotics, *i.e.*, proteins that interact with a membrane pore. Goodman *et*

al. teaches away from the claimed invention, a biologically active peptide that comprises D-amino acids. Goodman *et al*. disclose a drug that is conjugated to a spacer, which, in turn, is conjugated to a carrier. Goodman *et al*. disclose that D- amino acids can be included in the carrier, but that care should be taken to keep the bio-active site of the drug as far from the carrier as possible. Goodman *et al*. at column 10, lines 31-38. Thus, Goodman *et al*. teach away from a biologically active molecule that includes a D-amino acid at the active site. Neither Voet *et al*. or Goodman *et al*. specifically disclose or suggest an ADNF I protein that comprises at least one D-amino acid. Brenneman *et al*. disclose the ADNF I protein and its biological activity, but do not disclose the activity of an ADNF I protein that comprises at least one D amino acid residue. Thus, the cited references, alone or in combination, fail to disclose an ADNF I protein that has any D-amino acid residues. The references, alone or in combination, also fail to provide any motivation for one of skill to make an ADNF I protein that has D-amino acid residues.

The cited references fail to provide a reasonable expectation of success in synthesis of an ADNF I protein that has D-amino acid residues and that has neurotrophic/neuroprotective activity. Applicants respectfully remind the Examiner that the earliest priority date of the present application is August 18, 1999. At that time, mammalian proteins or peptides that included D-amino acids and had biological activity were extremely rare and were thought to be limited to proteins or peptides that acted on membrane pores.

As evidence of the state of the art at the time the invention was first reduced to practice, Applicants submit as Exhibit A Brenneman *et al*., *J. Pharmacol. & Exp. Med.* 309:1190-1197 (2004). The authors of Brenneman (2004), who include the inventors, discuss their motivation for synthesizing and investigating D-enantiomers of the ADNF I polypeptide at page 1195, right column. The authors made the D-enantiomers and fully expected to demonstrate that the D-enantiomers had no neuroprotective properties, thus, the authors state in a peer-reviewed journal that the results were unexpected. Even at the time Brenneman (2004) was published, *i.e.*, five years after the earliest priority date, the D-enantiomers of the ADNF I and III polypeptides were still the first reported neuroprotective agents to act in a non-stereoselective manner. See, *e.g.*, Brenneman (2004), page 1195, right column.

The references cited by the Office Action fail to provide those of skill with a reasonable expectation of success in generating a biologically active ADNF I protein that comprises D-amino acids. First, the references, alone or in combination, do not lead to an expectation that ADNF I is a protein that interacts with a membrane pore or that any protein that did not interact with a membrane pore would have biological activity if the protein sequence included D-amino acids. Moreover, the references, alone or in combination, do not provide an expectation that a neuroprotective protein, such as ADNF I, would be biologically active while comprising a D-amino acid. Without a reasonable expectation of success provided by the references, the Office Action cannot establish a *prima facie* case of obviousness.

In view of the above arguments and amendments, withdrawal of the rejection for alleged obviousness is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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